Remarks

I. Support for Amendments and Status of the Claims

The foregoing amendments to the specification have been required and/or suggested by the Examiner, are fully supported throughout the specification as filed, and add no new matter. In addition, by the foregoing amendments, claims 5 and 9-19 have been cancelled without prejudice or disclaimer as being drawn to non-elected restriction groups; claim 4 has been cancelled without prejudice or disclaimer; and claims 1-3 and 6-8 are sought to be amended. Support for the amendments to the claims can be found in the specification, *inter alia* at pages 3-6; throughout the Examples, particularly at pages 14-19; and in claims 10-19 as originally filed.

Hence, these amendments to the specification and claims add no new matter, and their entry and consideration are respectfully requested. Upon entry of the foregoing amendments, claims 1-3 and 6-8 are pending in the application, with claims 1 and 6 being the independent claims.

II. Summary of the Office Action

In the Office Action, the Examiner has made two objections to the specification, and one objection to and eight rejections of the claims. Applicants respectfully offer the following remarks to overcome and/or traverse each of these elements of the Office Action.

III. The Objections to the Specification

The Examiner has made two objections to the specification, and has required correction. Applicants respectfully offer the following remarks concerning these objections.

The Examiner has first objected to the specification for allegedly containing a title that "is not descriptive." Paper No. 10 at page 2, section 3.A. The Examiner goes on to suggest the beginning of a title that would apparently be acceptable. *See id.* By the foregoing amendments, the title of the present application has been amended to incorporate the Examiner's suggested language. It is therefore respectfully believed that this objection to the specification has been overcome; reconsideration and withdrawal are therefore respectfully requested.

The Examiner next objects to the specification for containing an error at page 2, line 17, which reads "p120/p120 dephosphorylation." *See* Paper No. 10 at page 2, section 3.B. Applicants thank the Examiner for calling this minor and obviously unintentional typographical error to their attention. By the foregoing amendments, the specification has been amended such that the text at page 2, line 17, now reads "p120/p100 dephosphorylation," as was clearly intended by Applicants and as suggested by the Examiner. Hence, it is believed that this objection to the specification has been overcome; reconsideration and withdrawal are respectfully requested.

IV. The Objection to Claim 4

In the Office Action at page 3, section 4, the Examiner has objected to claim 4 for alleged improper language in its dependency. By the foregoing amendments, and for reasons

unrelated to this objection, claim 4 has been cancelled. Thus, this objection has been rendered moot.

V. The First Rejection Under 35 U.S.C. § 101

In the Office Action at page 3, section 5.A., the Examiner has rejected claims 1-4 and 6-8 under 35 U.S.C. § 101 for allegedly being directed to non-statutory subject matter. By the foregoing amendments, claim 4 has been cancelled without prejudice or disclaimer, thus rendering moot the portion of this rejection that may have applied to claim 4. Applicants offer the following remarks concerning the application of this rejection to the remaining claims.

In making this rejection, the Examiner notes that claims 1-3 as filed recite "the use of," which allegedly is non-statutory language. Paper No. 10 at page 3, section 5.A. The Examiner has further suggested that "[t]he claims should be amended to recite, for example, 'A method of ...'" *Id.* By the foregoing amendments, independent claims 1 and 6 have been amended to recite "[a] method of," and dependent claims 2, 3, 7 and 8 have been amended to recite "[t]he method of claim [1 or 6]." Applicants respectfully assert that by these amendments, claims 1-3 and 6-8 are directed to statutory subject matter. Reconsideration and withdrawal of this rejection therefore are respectfully requested.

VI. The Second Rejection Under 35 U.S.C. § 101

In the Office Action at pages 3-4, section 5.B., the Examiner has rejected claims 1-4 and 6-8 under 35 U.S.C. § 101 for alleged lack of utility. By the foregoing amendments, claim 4 has been cancelled without prejudice or disclaimer, thus rendering moot the portion

of this rejection that may have applied to claim 4. Applicants respectfully traverse this rejection as it may be applied to the remaining claims.

In making this rejection, the Examiner contends that:

> These claims are directed to methods of using VEGF to screen for substances which affect the phosphorylation states of p120 and p100. However, the invention encompassed by these claims has no apparent or disclosed patentable utility. . . . To identify compounds which are involved in dephosphorylation in endothelial cells, for example, is not a specific or substantial use.

Paper No. 10 at page 3, section 5.B., lines 2-5 and 8-9. Applicants respectfully disagree with these contentions.

As currently presented, independent claim 1 (and hence, claims 2 and 3 that depend directly or ultimately therefrom) is drawn to methods of screening for substances capable of affecting the phosphorylation state of p120 and/or p100. Analogously, independent claim 6 as currently presented (and hence, claims 7 and 8 that depend directly or ultimately therefrom) is drawn to methods of screening for a substance capable of interfering with a VEGF-initiated pathway regulating p120/p100 serine/threonine phosphorylation. The present specification provides ample disclosure of the usefulness of such methods.

For example, the specification clearly states that the phosphorylation state of p120 and/or p100, and the regulation of p120/p100 serine/threonine phosphorylation via a VEGF-initiated pathway, may be important in pathologies involving cancer and hypoxia and for reducing oedema. *See, e.g.*, specification at page 4, lines 4-5; and at page 5, line 20, to page 6, line 6. Moreover, the present specification clearly states that the presently claimed methods

can be used as diagnostic tests useful for making therapeutic decisions or reporting on the efficacy of therapeutic drugs. *See* specification at page 4, lines 5-7, and at page 6, lines 11-15.

As the Federal Circuit has stated, "[t]he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999) (citing, *inter alia*, *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the claimed [invention] must be totally incapable of achieving a useful result."). As noted above, the present specification clearly teaches at least one identifiable benefit and/or useful result obtainable using the presently claimed methods. Hence, Applicants respectfully contend that the presently claimed invention is supported by a specific, substantial and credible asserted utility.

In view of the foregoing remarks, reconsideration and withdrawal of the utility rejection of claims 1-3 and 6-8 under 35 U.S.C. § 101 are respectfully requested.

VII. The Rejection Under 35 U.S.C. § 112, First Paragraph

In the Office Action at page 4, section 6, the Examiner has rejected claims 1-4 and 6-8 under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled by the specification as filed. By the foregoing amendments, claim 4 has been cancelled without prejudice or disclaimer, thus rendering moot the portion of this rejection that may have applied to claim 4. Applicants respectfully traverse this rejection as it may be applied to the remaining claims.

In making this rejection, the Examiner refers to the utility rejection discussed above, and contends that:

> since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Paper No. 10 at page 4, section 6, lines 3-5. Applicants respectfully disagree with these contentions.

As discussed in detail above, the presently claimed invention is clearly supported by a specific, substantial and credible asserted utility. Hence, to the extent that the present enablement rejection is based on any asserted lack of utility of the presently claimed invention, the enablement rejection is in error and should be withdrawn.

Applicants remind the Examiner that the enablement requirement of 35 U.S.C. § 112, first paragraph, is satisfied if the claimed invention is enabled so that any person skilled in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). To this end, the Federal Circuit has held that:

> [t]he purpose of [the enablement] provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and knowledge in the art.

Scripps Clinic & Research Foundation v. Genentech, Inc., 18 USPQ2d 1001, 1006 (Fed. Cir. 1991). Therefore, the Examiner is respectfully reminded that the proper standard of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the application, coupled with information known in the art, without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert.*

denied, 107 S. Ct. 1606 (1987). It is requested that in reconsidering this rejection, the Examiner also keep in mind that the question of undue experimentation is a matter of degree, and "the key word is 'undue,' not 'experimentation.'" *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), quoting *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation must not be unduly extensive. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), citing *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 224 USPQ 409, 413 (Fed. Cir. 1984).

The present specification clearly teaches how to use the presently claimed methods to obtain information regarding the ability of a substance to affect the phosphorylation state of p120/p100 and/or to interfere with a VEGF-initiated pathway regulating p120/p100 phosphorylation. *See, e.g.*, Examples 1-7 at pages 12-21, and the "Methods" section at pages 8-12. As discussed in detail above, the presently claimed methods also are supported by a specific, substantial and credible utility that would be readily recognized by one of ordinary skill in the art. Since the present specification provides significant guidance on how to use the claimed methods, which have been shown above to be supported by a specific, substantial and credible utility, Applicants respectfully assert that one of ordinary skill could readily perform the claimed methods without the need for undue experimentation.

In view of the foregoing remarks, Applicants respectfully assert that the specification fully enables the presently claimed invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

VIII. The Rejection Under 35 U.S.C. § 112, Second Paragraph

In the Office Action at page 4, section 7, the Examiner has rejected claims 1-4 and 6-8 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. By the foregoing amendments, claim 4 has been cancelled without prejudice or disclaimer, thus rendering moot the portion of this rejection that may have applied to claim 4. Applicants respectfully traverse this rejection as it may be applied to the remaining claims.

In making this rejection, the Examiner contends that the claims are indefinite as being incomplete for omitting essential steps, such as:

> methods of how to perform the claimed screening method, including a sequential order of step as well as a recitation of the proper controls and a conclusion step which demonstrates that the claimed method has been completed.

Paper No. 10 at page 4, section 7, lines 7-9. By the foregoing amendments, independent claims 1 and 6 have been amended to recite discrete taken in performing the claimed methods, including a recitation of controls and a conclusion demonstrating that the claimed method had been completed. Hence, Applicants respectfully contend that the present claims particularly point out and distinctly claim the subject matter regarded by Applicants as the invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, are respectfully requested.

IX. The Rejection Under 35 U.S.C. § 102(b) Over Esser

In the Office Action at pages 4-5, section 8.A., the Examiner has rejected claims 1-4 under 35 U.S.C. § 102(b) as allegedly being anticipated by Esser *et al.*, *J. Cell Sci. 111*:1853-1865 (1998) (Document "U" cited on the Form PTO-892 attached to Paper No. 10; hereinafter "Esser"). By the foregoing amendments, claim 4 has been cancelled without prejudice or disclaimer, thus rendering moot the portion of this rejection that may have applied to claim 4. Applicants respectfully traverse this rejection as it may be applied to the remaining claims.

In making this rejection, the Examiner states that Esser uses compounds such as placental growth factor ("PlGF," more specifically the VEGFR-1 ligand PlGF152) "to determine their effects on phosphorylation . . . . " Paper No. 10 at page 4, final two lines. This characterization of the disclosure of Esser, however, is irrelevant to the patentability of the claims as currently presented. In Esser, PlGF152 was used as a pharmacological tool to determine the pathway of VEGF signalling. *See, e.g.*, Esser at page 1858, and at pages 1860-1861. However, as noted in Esser, treatment of cells with PlGF152 "had no effect on the tyrosine phosphorylation pattern." Esser at page 1858, col. 2, final two lines. Hence, PlGF152 was used in Esser as a control to compare the effect of this substance on p120 with that of VEGF on p120. Importantly, however, at no time in Esser were cells treated with *both* VEGF *and* PlGF152. It is at least this last point that distinguishes the disclosure of Esser from the presently claimed invention.

Claims 1-3 as currently presented are drawn to methods of screening for substances capable of affecting the phosphorylation state of p120 and/or p100 using two populations of cells: a first population treated only with VEGF (the control population), and a second population treated with *both* VEGF *and* the test substance. Analogously, claims 6-8 as currently presented are drawn to methods of screening for substances capable of interfering with a VEGF-initiated pathway regulating p120/p100 serine/threonine phosphorylation using two populations of cells: a first population treated only with VEGF (the control population), and a second population treated with *both* VEGF *and* the test substance. Hence, in both claim sets, at least one population of cells is treated with VEGF *and* with the test substance. Such a scenario is not disclosed in Esser, where PlGF152 is used as an *alternative* to VEGF, rather than *in combination with* VEGF. Thus, Esser does not expressly disclose all of the elements of the presently claimed methods.

Under 35 U.S.C. §102, a claim can only be anticipated if every element in the claim is disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). As discussed above, Esser does not disclose every element in the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection under 35 U.S.C. § 102(b).

Applicants also wish to comment upon the Examiner's remarks at the top of page 5 of the Office Action, wherein the Examiner contends that:

> [t]he reference is silent as to whether or not serine or threonine residues are (de)phosphorylated. Therefore, since p100/p120 contain these residues, it would be expected that, in absence of evidence to the contrary, these residues would be (de)phosphorylated.

Paper No. 10 at page 5, lines 1-3. Applicants respectfully disagree with these contentions.

In making these contentions, the Examiner appears to assert that Esser *inherently* discloses the claimed invention (or, at least, that Esser inherently discloses (de)phosphorylation of serine and threonine residues). Applicants respectfully disagree with this assertion, and wish to remind the Examiner that "[i]n order for a disclosure to be inherent . . . the missing descriptive matter must necessarily be present in the [cited reference] such that one skilled in the art would recognize such a disclosure." *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998). Moreover, to rely on an inherency argument, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (PTO Bd. Pat. App. Int. 1990) (emphasis in original). That is, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991). In the present case, the Examiner has pointed to no disclosure in Esser that is "necessarily present" such that it would be recognized as by one of ordinary skill as disclosing the (de)phosphorylation of serine and threonine residues (thus, the *Tronzo* standard is not met by Barnes). As one of ordinary skill would understand, other amino acids besides serine and threonine can be (de)phosphorylated as a result of treatment with a given substance. In fact, the entire disclosure of Esser relates to changes in the phosphorylation state of *tyrosine* residues, rather than serine and threonine. Hence, based on the disclosure of Esser, one of ordinary skill would have no information relating to possible serine or threonine

(de)phosphorylation since, as the Examiner acknowledges, Esser is silent on this issue. Accordingly, any change in the phosphorylation state of p120 and p100 reported in Esser may have absolutely nothing to do with (de)phosphorylation of serine and threonine residues. Thus, the Examiner has pointed to no disclosure in Esser, and has provided no sound scientific reasoning, to support the notion that the missing disclosure in Esser "*necessarily* flows" from what *is* disclosed in Esser (hence, the *Levy* standard is not met by Esser). Finally, one of ordinary skill reading Esser could find no disclosure indicating that it was even possible, let alone probable, that serine and threonine residues were (de)phosphorylated by VEGF, PlGF152, or any other substance tested therein (thus, the *Continental Can* standard is not met by Esser). Hence, any attempted reliance upon inherent anticipation in making this rejection is factually and legally unfounded.

In view of the foregoing remarks, Applicants respectfully assert that Esser does not anticipate claims 1-3 as currently presented. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Esser therefore are respectfully requested.

X. The Rejection Under 35 U.S.C. § 102(e) Over Staddon

In the Office Action at page 5, section 8.B., the Examiner has rejected claims 1-4 under 35 U.S.C. § 102(e) as allegedly being anticipated by Staddon *et al.*, U.S. Patent No. 6,312,686 (Document "A" cited on the Form PTO-892 attached to Paper No. 10; hereinafter "Staddon"). By the foregoing amendments, claim 4 has been cancelled without prejudice or disclaimer, thus rendering moot the portion of this rejection that may have applied to claim 4. Applicants respectfully traverse this rejection as it may be applied to the remaining claims.

As was the case for the rejection over Esser discussed above, in making the present rejection the Examiner points to disclosure in Staddon that is irrelevant to the patentability of the claims as currently presented. Staddon discloses methods for modulating the permeability of physiological barriers, *e.g.*, by administering an effective amount of an agent that promotes tyrosine dephosphorylation of p100 or p120. As was the case for Esser, however, Staddon does not disclose the treatment of cells with *both* VEGF *and* an agent that affects the phosphorylation state of p120 and/or p100. It is at least this last point that distinguishes the disclosure of Staddon from the presently claimed invention.

As discussed above, the claims as currently presented are drawn to screening methods that use two populations of cells: a first population treated only with VEGF (the control population), and a second population treated with *both* VEGF *and* the test substance. Hence, in the presently claimed invention, at least one population of cells is treated with VEGF *and* with the test substance. Such a scenario is not disclosed in Staddon; indeed, VEGF is only mentioned in passing in that reference as an agent that activates tyrosine kinases (*see* Staddon at col. 14, lines 7-9). Thus, Staddon does not expressly disclose all of the elements of the presently claimed methods, and therefore cannot support a rejection under 35 U.S.C. § 102(b) in view of *Kalman*.

Applicants also note that the Examiner makes the same remarks relating to possible inherent disclosure in Staddon that were made in support of the rejection over Esser above:

> [t]he reference is silent as to whether or not serine or threonine residues are (de)phosphorylated. Therefore, since p100/p120 contain these residues, it would be expected that, in absence of evidence to the contrary, these residues would be (de)phosphorylated.

Paper No. 10 at page 5, section B., lines 9-11. Applicants respectfully disagree with these contentions for the reasons discussed above regarding these same contentions relating to Esser: the Examiner has pointed to no disclosure in Staddon that meets the standards for inherent anticipation under *Tronzo*, *Continental Can* and *Levy*. Hence, any attempted reliance upon inherent anticipation in making this rejection is factually and legally unfounded.

In view of the foregoing remarks, Applicants respectfully assert that Staddon does not anticipate claims 1-3 as currently presented. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e) over Staddon therefore are respectfully requested.

XI. The Rejection Under 35 U.S.C. § 103(a)

In the Office Action at pages 5-6, the Examiner has rejected claims 1-4 and 6-8 under 35 U.S.C. § 103(a) over either Esser or Staddon each in view of Ratcliffe *et al.*, *J. Biol. Chem.* *272*:31894-31901 (1997) (Doc. "V" cited on the Form PTO-892 attached to Paper No. 10; hereinafter "Ratcliffe"). By the foregoing amendments, claim 4 has been cancelled without prejudice or disclaimer, thus rendering moot the portion of this rejection that may have applied to claim 4. Applicants respectfully traverse this rejection as it may be applied to the remaining claims.

As an initial matter, Applicants respectfully contend that the portion of this rejection under 35 U.S.C. § 103(a) that may be based upon the disclosure of Staddon is in error, since Staddon is not available as prior art against the present application under 35 U.S.C. §§ 103(a) and (c). Effective November 29, 1999, "[s]ubject matter developed by another person, which qualifies as prior art only under subsection (e), (f), and or (g) of section 102 of this title, shall

not preclude patentability under [35 U.S.C. § 103] where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person." 35 U.S.C. § 103(c). This statutory provision "applies to all utility, design and plant patent applications filed on or after November 29, 1999, including continuing applications filed under 37 C.F.R. 1.53(b), continued prosecution applications filed under 37 C.F.R. § 1.53(d), and reissues." MPEP § 706.02(l)(1) (February 2003). Applicants note that Staddon and the present invention were, at the time the present invention was made, owned by or subject to an obligation of assignment to a common assignee: Eisai Co., Ltd. (*see* face page of Staddon, and the Assignment recorded on December 12, 2001, in the USPTO against the present application beginning at Reel No. 012362, Frame No. 0198). The present application is the U.S. national phase of International Application No. PCT/GB99/04162, filed on December 10, 1999, which designated the United States. Hence, under 35 U.S.C. §§ 120 and 363, the effective filing date of the present application is December 10, 1999, *i.e.*, after the effective date of November 29, 1999, of 35 U.S.C. § 103(c). Accordingly, the provisions of 35 U.S.C. § 103(c) are applicable to the present application.

Applicants respectfully assert that Staddon would qualify as prior art (if at all) only under 35 U.S.C. §102(e), as acknowledged by the Examiner in the present Office Action. Hence, under 35 U.S.C. §103(c), the disclosure of Staddon is not available as prior art for purposes of a rejection under 35 U.S.C. § 103 against the present application. This portion of the §103(a) rejection therefore is in error and should be withdrawn.

Notwithstanding the impropriety of the use of Staddon in the present rejection, Applicants reiterate and incorporate herein the remarks made above concerning the disclosures of Esser and Staddon. These documents are seriously deficient as primary references for use in an obviousness rejection, since neither of these references discloses, suggests, or otherwise contemplates the treatment of cells with *both* VEGF *and* an agent that affects the phosphorylation state of p120 and/or p100. Hence, Esser and Staddon are not useful as primary references in the attempt to establish a *prima facie* case of obviousness. These deficiencies in Esser and Staddon are not cured by the disclosure of Ratcliffe, which also does not disclose the treatment of cells with *both* VEGF *and* an agent that affects the phosphorylation state of p120 and/or p100.

Thus, the references cited by the Examiner in making this rejection fail to teach all of the elements of Applicants' claims. Therefore, it follows that a combination of the disclosures of these references would *not* lead one of ordinary skill in the art to Applicants' claimed invention. Notwithstanding this fact, Applicants also contend that neither the references themselves, nor the knowledge generally available to those of ordinary skill in the art, provide a suggestion or motivation to modify the cited references or to combine the disclosures of these references in such a way that would have rendered the claimed invention obvious.

The Examiner provides the following explanation as to why the skilled artisan would allegedly be motivated to combine the teachings of Esser and/or Staddon with that of Ratcliffe:

> Neither Esser nor Staddon teach a PKC pathway. However, Ratcliffe do teach that p100/p120 are dephosphorylated in response to PKC activation. Therefore it would have been obvious for one of ordinary skill in the art at the time of the

> present invention to have performed a screening assay using VEGF and a PKC pathway to screen for competitors and activators of VEGF.

Paper No. 10, at page 5, section 9, lines 12-16. However, this attempted explanation appears to misconstrue the standard for obviousness and whence the required motivation must arise in order for a *prima facie* case of obviousness to be established. Applicants respectfully remind the Examiner that the requisite motivation for establishing a *prima facie* case of obviousness *must* be found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *See In re Kotzhab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). Moreover, the mere fact that an advantage *might* be realized by combining reference teachings does not mean that a skilled artisan would be motivated to do so. *See In re Mills*, 916 F.2d 680,682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1992) (although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so."). In the present case, rather than pointing to anything specific in the references or in the general knowledge of those skilled in the art, the Examiner has simply asserted that it would have been obvious to perform "a screening assay using VEGF and a PKC pathway to screen for competitors and activators of VEGF." This assertion does not provide, nor rely upon, the proper motivation required to combine the cited references. Moreover, the Examiner has pointed to no acceptable objective evidence or sound scientific reasoning that would provide such motivation. Instead, the Examiner appears to *assume* that such motivation exists in the general knowledge of those of ordinary skill, without providing any basis for such an assumption. As discussed above, the requisite motivation must be found either in the prior art or in knowledge that is generally

available to those of ordinary skill in the art; a baseless *assumption* of such knowledge is legally impermissible under *Fine* and *Kotzhab*. Moreover, as the Federal Circuit has held:

> [t]he range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence."

In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999) (citations omitted). Since the Examiner has provided no actual evidence to support the conclusory statement that Esser or Staddon, along with Ratcliffe, would have rendered the present invention obvious, Applicants respectfully assert that a *prima facie* case of obviousness has not been established.

It therefore appears that the Examiner is attempting to find the required motivation to combine the cited references in Applicants' own specification rather than in the cited art. As the Federal Circuit has held numerous times, however, such a hindsight analysis is impermissible -- instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) ("When prior art references require selective combination by the [fact-finder] to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself."); *Fine*, 5 USPQ2d at 1600 ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); *In re Pleuddemann*, 910 F.2d 823, 828 (Fed. Cir. 1990) (noting that use of an applicant's specification as though it were prior art to support an obviousness determination is legal error); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991)

(holding that both the suggestion to combine references, and a reasonable expectation of success in making the claimed invention, "must be founded in the prior art, not in the applicant's disclosure."). The Board has also provided the same mandate on this issue:

> it is impermissible to use the claimed invention as an instruction manual or "template" to piece together isolated disclosures and teachings of the prior art so that the claimed invention may be rendered obvious . . . . a rejection based on § 103 must rest on a factual basis, with the facts being interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, the examiner has the initial duty of supplying the factual basis for the rejection he advances. He may not, because he doubts that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

Ex parte Haymond, 41 USPQ2d 1217, 1220 (Bd. Pat. App. Int. 1996). Thus, the use of hindsight analysis in the present case is impermissible and cannot be used to attempt to establish a *prima facie* case of obviousness.

Finally, Applicants are aware that the Examiner may consider the motivation to combine the cited references as "inherent" in the knowledge of one of ordinary skill in the art, particularly in view of the Examiner's remarks in the sentence bridging pages 5-6 of the Office Action that are reminiscent of those discussed above in the § 102 rejections over Esser and Staddon. Applicants wish to remind the Examiner, however, that there is no such thing as "inherent obviousness," since inherence and obviousness are different legal concepts. *See In re Spormann*, 150 USPQ 449, 452 (C.C.P.A. 1966). That which is inherent cannot be obvious, since inherent information "is not necessarily known . . . . [and] Obviousness cannot be predicated on what is unknown." *Id.* Since the present rejection is based on obviousness, any contention by the Examiner that is based on the possible presence of inherent knowledge

in the art (either in the cited references or in the general knowledge of those of ordinary skill) must necessarily fail.

Applicants submit that, upon careful analysis of the cited references, the skilled artisan would have found no motivation to combine or modify the reference teachings to arrive at a tumor vaccine that falls within the scope of the present claims. Accordingly, a *prima facie* case of obviousness has not been established. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

XII. The Double-Patenting Rejection

In the Office Action at page 6, section 10, the Examiner has provisionally rejected claims 1-4 and 6-8 under the judicially created doctrine of obviousness type double-patenting over all of the claims of commonly owned, co-pending U.S. Appl. Nos. 10/349,111 ("the '111 application") and 10/349,074 ("the '074 application"). By the foregoing amendments, claim 4 has been cancelled without prejudice or disclaimer, thus rendering moot the portion of this rejection that may have applied to claim 4. Applicants respectfully traverse this rejection as it may be applied to the remaining claims, because the rejection has been made in error.

Applicants note that both the '111 application and the '074 application are divisionals of the present application filed under 35 U.S.C. § 121. These divisional applications were filed as a result of a restriction requirement issued by the previous Examiner in the present application on September 3, 2002 (Paper No. 7). The present Examiner reaffirmed this Restriction Requirement in the present Office Action (*see* Paper No. 10 at page 2, section 1.A).

In the Restriction Requirement, the Examiners established three restriction groups: Group I (claims 1-4 and 6-8), which was elected for prosecution in the present application; Group II (claims 5, 9 and 19); and Group III (claims 10-18). Upon filing of the '111 and '074 applications on January 23, 2003, the claims in the two applications were amended such that the '111 application contained only claims 5, 9 and 19 (*i.e.*, restriction group II) originally filed in the present application, while the '074 application contained only claims 10-18 (*i.e.*, restriction group III) originally filed in the present application. Hence, the present application, and the '111 and '074 divisional applications, can be considered to be prosecuting claims that were restricted into separate groups in a restriction requirement issued in the present application.

An obviousness type double-patenting rejection is improper if it is based upon a divisional application filed as a result of a restriction requirement:

> A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.

35 U.S.C. § 121 (Feb. 2003). *See also* MPEP § 804.01. As noted above, a restriction requirement was issued in the present application, and the '111 and '074 divisional applications were "filed as a result of such a requirement." Moreover, both the '111 and '074 divisional applications were filed "before the issuance of the patent" on the present application. Hence, under 35 U.S.C. § 121, these applications are not available as references for use in making an obviousness type double-patenting rejection in the present "original

application." Therefore, Applicants respectfully assert that the obviousness type double-patenting rejection has been made in error; reconsideration and withdrawal are respectfully requested.

XIII. Other Matters

Applicants note that the Examiner has lined through Doc. No. AT24 (U.S. Appl. No. 09/848,353, filed May 4, 2001 ("the '353 application)) listed on the Form PTO-1449 filed with the Information Disclosure Statement filed in the present matter on December 12, 2001. In refusing to consider this reference, the Examiner states that "it is not proper subject matter for an IDS." Paper No. 10 at page 2, Section 2.A.

The '353 application is a continuation application, filed under 35 U.S.C. § 1.53(b), of U.S. Appl. No. 08/648,182, which issued on November 6, 2001, as U.S. Patent No. 6,312,686 (*i.e.*, the Staddon patent cited by the Examiner as Doc. "U" on the Form PTO-892 attached to Paper No. 10, and relied upon by the Examiner throughout the Office Action). Hence, Applicants respectfully believe that their duty of disclosure under 37 C.F.R. § 1.56 has been fulfilled with respect to the '353 application as filed, since any information contained therein that may be material to the present application has already been considered by the Examiner by citation of and reliance upon Staddon.

However, as suggested by the Examiner in the Office Action at page 2, Section 2.A., and in the interests of complete candor under 37 C.F.R. § 1.56, Applicants wish to call the Examiner's attention to the '353 application, such that the information contained therein, although not yet published, can be considered without being printed on an IDS. Applicants

note that the two inventors in the present application are also inventors on the '353 application, and that the '353 application and the present application are commonly owned by Eisai Co., Ltd. Early notification that the '353 application has been considered therefore is respectfully requested.

Conclusion

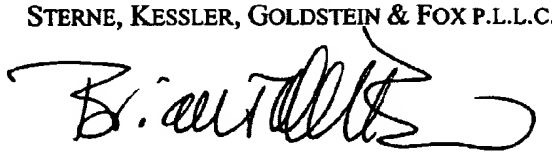
All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the outstanding objections and rejections, and allow all pending claims.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt consideration of the foregoing amendments and remarks, and allowance of all pending claims, are earnestly solicited.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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